INTRATHECAL OR INTRAVENTRICULAR GENTAMICIN IN GRAM-NEGATIVE BACILLARY MENINGITIS

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INTRATHECAL OR INTRAVENTRICULAR GENTAMICIN IN GRAM-NEGATIVE BACILLARY MENINGITIS

BY

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Introduction

Gentamicin has its origins in Jamesville, N.Y. mud and Syracuse, N.Y. park loam. At least the micro-organisms which produce gentamicin, Micromonospora echinospora and Micromonospora purpura, were isolated from these mud and loam specimens. This new antibiotic complex was first reported in 1963 by Weinstein, Luedemann, Oden and Wagman (1). In a later article the same authors characterized this drug as a basic, stable, water soluble, and broad spectrum antibiotic complex which was extracted by cationic exchange resin and differentiated from other similarly extracted antibiotics by comparative paper chromatography.

In vitro efficacy: Weinstein, et al. (1) reported an increased unit potency of gentamicin over kanamycin or neomycin in mice infected with Klebsiella pneumonia, Staphlococcus auerus, Salmonella schottmuelleri, Diplococcus pneumoniae, Pseudomonas aeruginsoa, and Streptococcus pyogenes. At the same time, White (2) reported in vitro inhibition of between 20 and 60 strains each of Staphlococci, Proteus, Psuedomonas, E. coli and Aerobacter aerogenes with a gentamicin concentration of 4 µg/ml. Ninety-five percent of all strains were inhibited by this concentration except for Proteus which required 15µg/ml to inhibit all species. Bactericidal levels were observed to be within two tube dilutions of bacteriostatic concentrations. Also during 1964, Klein,

Eickhoff, and Finland (3) reported *in vitro* inhibition of most Staphlococci, Salmonella, Herella, and *Klebsiella-aerobacter* with a concentration of 3.1µg/ml whereas 6.2-25ug/ml were required to inhibit *E. coli*, Meningococci, Streptococci, *Diplococcus pneumoniae*, *Ps. Aeruginosa*, and Proteus. By 1970, Rubenis, Kazij and Jackson (4) had tested approximately 100 strains each of Klebsiella, Aerobacter, Psuedomonas, *E. coli*, and Proteus species and found the minimum inhibitory concentrations (MIC's) of gentamicin to be 0.8, 1.6, 3.1, and 12,5 µg/ml respectively. Weinstein, et al. (1) noted that strains of *E. coli* and *S. Aureus* resistant to streptomicin and streptothricin were sensitive to gentamicin but that those resistant to kanamycin and neomycin were also resistant to gentamicin. Klein, et al. (3) reported that organisms resistant to streptomycin, kanamycin or neomycin were sensitive to gentamicin whereas those made resistant to gentamicin were resistant to the other aminoglycosides as well. These authors felt this was evidence for possible "unidirectional cross resistance." As can be imagined, these initial reports of marked activity of this drug against gram-negative organisms as well as against many gram-positive bacteria quickly stimulated investigations into the methods of action and excretion, the dose/concentration relationship, and the possible toxicities of gentamicin.

Mechanism of action: Rosselet and co-workers (5) initially characterized the antibiotic complex as an aminoglycoside. Rinehart (6) later termed gentamicin an "aminoglycosidic aminocyclitol."

This term refers to any compound in which a sugar containing an amino group is attached via a glycosidic linkage (amino-glycoside) to another fragment containing a cyclitol unit where one or more hydroxyls are replaced by amino groups (amino-cyclitol). Two subclasses exist, one containing streptidine- (streptomycins), and the other containing deoxystreptanine- (neomycins, kanamycins, paromycins and gentamicin). The exact mechanism of action of these antibiotics has yet to be elucidated, although arrest of protein biosynthesis within minutes following the addition of gentamicin was observed by Hahn and Sarre (7). These investigators commented, "The finding that nucleic acid biosynthesis is relatively unaffected by gentamicin renders observations on the failure of protein synthesis highly significant. We conclude that gentamicin is a specific inhibitor of protein biosynthesis in susceptible bacteria" (7). Because gentamicin shares many common features with streptomycin concerning effects on cell protein synthesis (8), Davies has observed (9) that its mechanisms of action may mimic that of streptomicin which binds to the 305 ribosomal subunit, interferes with the function of the A site and prevents irreversibly further protein synthesis (10). Lorian notes that gentamicin interferes with the translation mechanism producing a misreading by messenger RNA which results in a nonsense polypeptide (11).

Resistance: Consistent with the above mechanism, is the finding that gentamicin resistant mutants have been isolated which produce altered ribosomal proteins (9). Resistant pseudomonas species utilizing this mechanism have been isolated in burn wound units (12). More commonly, resistance in clinical situations is due to the presence of extra chromosomal elements, R-factors, which enzimatically deactivate gentamicin by esterification or hydroxyl groups or acetylation of amino groups (9).

Serum levels: Black, Calesnick, Williams and Weinstein (13) found peak serum levels occurred one hour after injection of 0.2-3.2 mg/kg intramuscularly (IM) into healthy human subjects. Activity could still be demonstrated 6 hours later with the low doses and 12 hours later with high doses. The peak blood level in micrograms per milliliter was generally four to six times the administered dose in milligrams per kilogram. Both Black, et al. (13) and Riff and Jackson (14) found that approximately 30% of gentamicin was bound by serum proteins. Riff and Jackson (14) used radioactivity labeled gentamicin (C^{14}) to demonstrate a 10% binding to erythrocytes such that each alteration of 4 hematocrit points inversely changes the serum level by 2 µg/ml. However, McCracken, Chrane & Thomas (15) found no correlation between peak serum levels of gentamicin and hematocrit in 58 infants under two weeks of age. They questioned whether this discrepancy might be due to a different affinity of fetal red blood cells for gentamicin.

No accumulation of the antibiotic was seen after repeated injections in normal subjects (13) or in patients with BUN $<$25 mg/100 ml (3). However, Klein, et al. (3) studied one patient who had a BUN of 105mg% at the end of a 9 day course of gentamicin therapy, and observed a serum level of 17ug/ml in this patient ten days after the final dose which suggested that impaired renal function resulted in prolonged serum concentrations.

Excretion: Initial renal clearance studies were carried out in the dog with low doses of gentamicin (1.39 and 1.76 mg/kg) which had no appreciable effect on urine flow, electrolyte excretion, creatinine clearance or glomerular filtration rate. The rate of clearance was approximately equal to the GFR and studies in humans showed almost complete recovery of the unchanged antibiotic within 24 hours following doses of 1.6 and 3.2 mg/kg (13). No other significant method of elimination was found. Gyselynck, Forrey and Cutler (16) did extensive studies on the pharmacokinetics of gentamicin in patients with differing degrees of renal function and observed that the renal clearance of gentamicin was similar to that of inulin. However, when the glomerular filtration rate was less than 20mg/min, renal excretion of gentamicin in 72 hours was less than 50% of the administered dose. McCracken's studies on excretion in infants and neonates demonstrated that percentage excreted was independent of weight but correlated directly with age and rates of creatinine clearance (17,18), and recommended a higher dose during the first week of life (7.5 rather than 5.0 mg/kg/day) (15).

Clinical trials: Four patients (a woman with burns complicated by Pseudomonas septicemia, a man with a staghorn caliculus and septicemia due to Proteus mirabilis, a third patient with septicemia due to Proteus and a fourth person with polycystic kidney disease and infection due to Pseudomonas) were treated with gentamicin in March 1962. The last patient was cured with gentamicin after other antibiotics had failed but was the first to develop vestubular toxicity. Jackson, when describing these patients in his introduction to the Symposium on Gentamicin, in 1969, observed, "Thus the scope of the problem was characterized in these first 4 patients; both by the need for gentamicin or other drugs to control infections, especially serious infections with gram-negative bacteria, and by some of the difficulties involved in the use of aminoglycoside antibiotics" p. 341 (19).

Gentamicin since its first clinical application in 1962 has been used for all types of gram-negative bacterial infections and for many infections caused by gram-positive organisms. It has often been the drug resorted to after other antibiotic failures, and has commonly been used in severe septicemias and urinary tract infections.

Use in Meningitis: Naturally then, gentamicin was tried in cases of gram-negative bacillary meningitis. Afflicted patients were usually neurosurgical patients, or neonates, often with

hydrocephalus or meningomyelocele, but the route of administration has varied considerably. Some patients have received only systemic (IM or IV) gentamicin, others have had gentamicin administered only intrathecally (IT), intraventricularly (IVt), or intracisternally (IC). Most patients with meningitis have received various combinations of systemic therapy and direct placement into cerebrospinal fluid (CSF). Rodrigues, et al. (20), found that systemically administered gentamicin does not readily enter the CSF when given to patients without inflamed meninges. In three of four patients receiving 3-4 mg/kg/day of gentamicin only intravenously, no CSF gentamicin activity was found despite peak serum concentrations of 2.6 to 5.2 µg/ml. In a CSF sample from the fourth patient drawn 3 hours after the IV infusion began, there was a concentration of 1.1 µg/ml. This level was approximately 20% of the patients' peak serum concentration observed one hour before the CSF sample was drawn. Riff and Jackson (14) found that in patients receiving systemic gentamicin without meningeal inflammation, CSF gentamicin levels were detectable only when serum levels were 4 µg/ml or higher.

Systemic use in infant meningitis: In contrast to the above data, several patients with meningitis have been successfully treated with only intramuscular gentamicin therapy. Klein, Eickhoff and Finland (3) described a prematurely born infant with a meningomyelocele who had been unsuccessfully treated for *Pseudomonas aeruginosa* meningitis with chloramphenicol and

polymyxin. At 5 weeks of age the infant began receiving 2mg/kg/day of gentamicin IM. Simultaneous serum and CSF samples, collected two hours after the last IM dose, had gentamicin levels of 0.73 and 0.53 µg/ml respectively and resulted in prompt sterilization of the ventricular fluid. In 1969, Nunnery and Riley (21) reported 9 cases of gram-negative bacillary meningitis in infants aged 1 day to 13 months treated with 1.2 mg/kg/day of IM gentamicin. Four infections were caused by Klebsiella-Enterobacter, 3 by Pseudomonas aeruginosa and 2 by E. coli. All the infections had not responded to multiple other antibiotics before gentamicin was begun. Seven infections responded favorably. One treatment failure occurred with Pseudomonas aeruginosa and the other with a Klebsiella infection. Two years later three infants with Proteus mirabilis and one infant with E. coli meningitis were described by Klein, et al. (22). These patients were given 3 mg/kg of gentamicin twice a day intramuscularly. One patient with a proteus infection died 18 hours after therapy was started, the second patient with proteus meningitis, had only 1 day of therapy due to parental withdrawal of consent. A third patient infected with E. coli, received 1 mg IT after failure to sterilize the CSF with only systemic gentamicin therapy. However, this particular ogranism later required chloramphenicol for eradication and was found to have a gentamicin MIC of 12.5 µg/ml. McCrakcen, Chrane and Thomas (15) treated seven neonatal meningitides with only systemic gentamicin, 6 with E. coli and 1 with Enterobacter infections. They reported obtaining sterile CSF in 3 within 36 hours. CSF in two others

had become sterile before switching to gentamicin but they clinically improved immediately with systemic therapy. Two additional infants required 5 and 7 days of treatment for CSF sterilization. These investigators stated that "the levels of gentamicin in cerebrospinal fluid following systemic administration were generally low (0.2-2.9 μg/ml) and directly related to the dosage and degree of meningal inflammation" p. S222 (15). They also found that the bactericidal titers of spinal fluid against the infecting organisms were consistenly 1:2 or less. In 1973, Zoumboulakis, et al. (23) presented data on 19 infants with gram-negative bacillary meningitis who had been treated with 3 mg/kg/day of systemic gentamicin after "initial" therapy with other antimicrobial agents had not resulted in improvement. Sixteen of these patients (10 E. coli, 2 Klebsiella, and 2 Proteus, 1 Pseudomonas and 1 mixed Pseudomonas and E. coli) had their infection "controlled" within 2-5 days of treatment with one systemic gentamicin. An infant with Klebsiella infection and one with Pseudomonas and E. coli meningitis died, and hydrocephalus developed in the infant infected with Pseudomonas. Serum and CSF gentamicin assays were not performed. The authors note that none of their patients received intrathecal or intraventricular gentamicin. They stated, "Nevertheless our results are comparable with those of the few studies in the literature in which gentamicin was used intrathecally and/or intraventricularly for the treatment of infantile meningitis" p. 57 (23).

Efficacy of gentamicin instillation into CSF: In order to evaluate the statement of Zoumboulakis, et al., it is necessary to examine the reports of direct instillation of gentamicin into the CSF. Leedom, et al. (24) studied four infants aged 14 days to 4 months who received intrathecal (IT) or intraventricular (IVt) gentamicin in doses from 0.01 to 1.0 mg/day. The infection was cured in one patient. Another patient had sterile CSF when gentamicin was started, but did resolve an abnormal glucose value on therapy. The third patient suffered a relapse, and the fourth infant failed to have sterile CSF after 9 days of IT therapy. These investigators pointed out that these four infants had received prior antibiotic regimens which had failed to cure their infections, and that they were older than the majority of neonates with meningitis. The authors also reviewed their experience with neonatal meningitis over the previous six years. Thirty-two of 54 infants with gram-negative bacillary infections died (59%). Seven survived with severe neurological impairment and 15 patients had no residual dysfunction (24). Newman and Holt (25) reported their experience with 12 cases of neonatal meningitis treated with gentamicin 1 mg/day intraventricularly and 2 mg/kg/day IM. In the first case, the authors titrated the CSF gentamicin concentration against the MIC (2 µg/ml) and MBC (5 µg/ml) of the infecting strain of Pseudomonas pyocyanea. An initial daily dose of 0.1 mg IVt and 1 mg/kg IM, was gradually increased to 1 mg IVt and 2 mg/kg IM on day 6 before adequate CSF levels of 3 µg/ml were attained.

However, CSF cultures were sterile three days after the initial dose. Two additional cases were similarly treated and required the same dosages. Nine additional cases were therefore treated with a standard dosage of 1 mg/day IVt and 2 mg/kg/day IM. Treatment was successful in nine of the 12 cases, 6 with Klebseilla, 2 E. coli (1 failure), 2 Ps. aeruginosa (both failures), 1 Ps. pyocyanea and 1 Proteus. These results caused the investigators to state "In our view, intraventricular treatment is essential, as effective CSF levels cannot be guaranteed with intramuscular administration alone." p. 475 (25). Two years later the same authors reported results (26) of 13 additional patients who had been "unselected" and in whom treatment of any type was "unlikely to succeed" in contrast to their earlier study (25) where, they now stated, patients were only treated with gentamicin if the MIC of the organism was low and other drugs were likely to be ineffective. The second group of thirteen patients resulted from their new hospital policy of treating all cases of clinical meningitis with IVt and IM gentamicin as soon as gram-negative organisms were found in the CSF. Six of these latter 13 patients died of overwhelming infection within 24 hours, receiving only one IVt dose. Three patients (1 Proteus, 2 coliform) were cured . Four patients were considered gentamicin failures, 2 of whom died (1 Proteus and 1 coliform) and 2 of whom were cured with other antibiotics (1 coliform and 1 Proteus). CSF gentamicin levels 24 hours after the intrathecal dose (24 hour CSF levels)

ranged between 6 and 1.0µg ml. They found lower levels on the first day. Unfortunately, the terms "intrathecal" and "intraventricular" were used interchangably in their report (26) and do not allow certainty concerning the route of administration for comparison with later disputes concerning the effective distribution of gentamicin within the subarachoid space. Laber, Kalthan and Mahgrefte (27) reported their results in treating meningitis in 14 infants born with spina bifida who received 0.5 to 8 mg/kg/day of IM gentamicin and 0.5 (2 cases) to 8 mg (10 cases) per day intraventricularly. These children had been started on a regimen of chloramphenicol IM and IVt and were changed to gentamicin a) if the organism was not sensitive to chloramphenicol, b) if a less toxic drug could be used, or c) because of failure to sterilize the CSF. Seven of the 14 died (3 infected with E. coli, 2 with Ps. pyocyanea, 1 with Proteus and 1 with Actinobacter anitratus). One infant with E. coli meningitis died later of other causes as did another infant infected with Mycoplasma pneumoniae, whereas another with E. coli lived but was retarded. Only four infants (2 Proteus, 1 E. coli, 1 Strep faecalis) survived without sequelae attributable to the ventriculitis. The MIC range of all organisms was 0.8-1.5 µg/ml, and 24 hour CSF levels varied from 0.5 to 130 µg/ml. Five of six infants with mean CSF levels below 6 µg.ml died, whereas six of eight with average levels above 6 µg/ml recovered from their infection. Despite CSF levels greater than 2 µg/ml and in excess of the MIC in 11 of

the 14 cases, increasing concentrations of gentamicin in the spinal fluid were directly associated with increasing cure rate. These authors observed that 24 hour CSF levels tended to rise as long as intraventricular therapy was given. Lorber, et al. (27) concluded that despite suboptimal doses in early patients, and delay caused by using another antibiotic initially, they had "fair success" in treating ventriculitis due to gram-negative organisms, and stated that gentamicin may be the initial drug of choice in such infections. Mathies, et al., (28) published results on 15 episodes of gram-negative bacillary meningitis, in 13 patients 11 of whom received intracisternal gentamicin. Six of these patients died but the CSF had been sterilized in 4 cases with 3 mg/kg/day IM and 1mg/day intracisternally. Three patients survived with severe sequelae and two recovered completely. One infant's E. coli infection was eradicated with systemic therapy and another with E. coli died after the first IM dose. Neither serum nor CSF assays were done in these cases. However, van der Waarde and van der Weil-Korstanje (29) reported CSF levels in a similar case, an infant born with spina bifida and afflicted with E. coli meningitis which was unresponsive to systemic kanamycin. Gentamicin at doses of 8 mg/kg/day IM and 8 mg/day IVt produced serum levels of 1.8 -5.0 µg/ml and CSF concentrations of 28-100 µg/ml and sterilized the CSF within 48 hours.

Any summary of the reports of gentamicin efficacy in curing infantile meningitis caused by gram-negative organisms is complicated not only by the diversity of patients and their vaguely

defined "host defenses," but also by the different infecting bacteria, and finally, by the method of administering the antibiotic in its range of dosages. In fact, the most salient features of these studies is the unpredictable nature of CSF concentrations of gentamicin in any one patient on a particular regimen. This feature leads to the firm conclusion that individual CSF and serum levels must be monitored for effective treatment of such a potentially lethal infection. Several less firm conclusions are that: 1) Gentamicin does enter the CSF from the systemic circulation better when the meninges are inflamed; 2) that systemic therapy may cure infantile meningitis but that IT or IVt therapy results in higher CSF levels more reliably; and 3) that higher levels, often regardless of the MIC, are associated with higher cure rates. Finally it should be noted that gentamicin's poorest record occurred in the treatment of Pseudomonas meningitis where over half of the reported cases (6 of 11) were treatment failures.

Gentamicin in Adult Meningitis: Although most series in the literature have been of neonatal or infantile meningitis, several case reports describe the use of gentamicin in adult CSF infection following trauma and/or neurosurgical procedures. Rubenfire, et al. (30) published a detailed account of the course of a 59 year old patient with recurrent olfactory groove meningioma and subdural empyema with CSF infection by Paracolobactrum aerogenoides sensitive only to Polymyxin B and gentamicin. Six days of ineffectual

Polymyxin B therapy was followed by IM, IT and "intra-abcess" (IA) gentamicin therapy over a 40 day course during which gentamicin levels in CSF, serum and abcess contents were monitored. Although these authors state that during meningeal inflammation CSF levels are 1/2 to 2/3 those of serum, data were not provided to support this conclusion since at no time was the patient receiving IM gentamicin without also IA or IT instillations. An IM injection of 40 mg was given 8 days after cessation of all antibiotic therapy when meningeal inflammation had subsided. At that time simultaneous serum and CSF levels revealed an approximate ratio of 1:4. McHenry, et al. (31) also used gentamicin after failure of other antibiotics in an 18 year old male with E. coli meningitis following trauma. Despite a systemic dose of 3 mg/kg/day, improvement was not seen until a subcutaneous CSF reservoir of the Ommaya type allowed direct instillation of gentamicin into the ventricles. Scheidemandel, et al. (32) reported a case of persistant E. coli meningitis which responded promptly to 10 mg/d of IT and 5 md/kg/d of IV gentamicin. The CSF grew E. coli once after this therapy was initiated but, after the epidural foreign body (a bullet) was removed, the CSF remained sterile with only IM gentamicin. Graybill, et al. (33) treated Enterobacter meningitis, which occurred in a 60 year old man following removal of a posterior fossa meningioma, with 5 mg of intraventricular gentamicin which caused a grand-mal seizure and respiratory arrest. Return to Polymyxin B therapy permitted return of positive CSF cultures which had been negative

for the 24 hours after the one gentamicin dose. Cautiously these investigators again used IVt gentamicin, only 1 mg/d, and the infection was cured without further side effects.

Occasionally, very high doses of gentamicin have been given to adult patients. Fasano, et al. (34) reported treating patients with 160 mg/d intrathecally without ill effect, and Smilack and McClosky (35) presented a case where a patient inadvertently received two doses of 160 mg of gentamicin intrathecally one day apart with no untoward effects except perhaps a mild radiculopathy. This patient had rapid sterilization of his CSF. As these case reports describe only cures, often unexpected, and provide no way of quantifying or characterizing treatment failures. These few reports, then, do little more than recommend a trial of gentamicin in adult meningitis caused by sensitive organisms.

Such a trial was carried out recently by Rahal, et al. (36) on 21 adult patients. Only twelve of these patients had culture proven meningitis, four with Pseudomonas aeruginosa, three with Klebsiella, two with Serratia marcescens, one with Hemophilus parainfluenzae and two with Diplococcus pneumoniae (who were treated with penicillin G after return of the culture results). All patients received other antibiotics in addition to IM and IT gentamicin. Although the authors do not give a failure or cure rate for the gentamicin regimen, they do mention 3 patients who died despite IT therapy. Several patients received daily doses of 8, 12, and 20 mg

IT, but most were treated IT with 4 mg/d. CSF concentrations were determined in 18 patients at various times after the 4 mg IT dose and were found to decrease rapidly over 24 hours such that concentrations at 10-15 hours varied from less than 1 µg/ml to 20 µg/ml while at 20 hours "two-thirds of the CSF levels were below 3 µg/ml." Unfortunately, the authors do not give the actual number of samples tested at this time but they did conclude that the IT dose should be given every 18 hours to maintain adequate CSF concentrations. It is not possible to determine the efficacy of gentamicin in adult meningitis from Rahal's results since these workers do not give data for the bacteriologically proven infections, even though they state that, "memingitis was clinically or bacteriologically eradicated from 16 of the remaining 19 patients; however 12 of these patients died of other causes during hospitalization." p. 1397 (36). Yet this report specifically details 4 deaths which occurred without CSF sterilization, and further states that "Eleven patients died within two months of treatment, primarily from the underlying disease." p. 1396 (36). Even though these numbers are confusing, gentamicin was shown in several instances to eradicate gram-negative bacillary meningitis, and some data concerning lumbar CSF concentrations plotted over time was obtained.

Distribution of Gentamicin in the CSF: In 1972, Moellering and Fisher (37) reported a 16 month old infant with Proteus morganii meningitis--treated first with IM gentamicin (6 mg/kg/d) which gave CSF levels of 0.5 and 0.3 µg/ml, and then with

intrathecal doses of 1 mg/d, which gave peak lumbar CSF levels of 6.9 µg/ml. However, three hours after an IT dose of 2 mg, lumbar CSF had a concentration of 10.3 µg/ml whereas a simultaneous ventricular CSF level was only 1.2 µg/ml. Culture of the two samples revealed sterile lumbar fluid but ventricular fluid was still infected with Proteus. Over the following five days, daily intraventricular doses of 2 mg gave adequate levels, 21-39 hours after injection, in both ventricular (2.4-10.0 µg/ml) and lumbar (3.1-5.0 µg/ml) CSF samples, and CSF cultures became negative within 24 hours. This is the only case report in the literature which provides simultaneous lumbar and ventricular CSF levels of gentamicin. It serves to highlight the controversy surrounding routes of antibiotic administration. It is clear from the above reports that injections of two or more milligrams of gentamicin into the CSF will reliably produce concentrations 24 hours later of greater than 2.5 µg/ml in fluid drawn from the same site. Documented cases of therapeutic failure with IT gentamicin followed by success with IVt administration demonstrate the unreliability of lumbar CSF concentrations as an index of adequate treatment. Animal studies have attempted to elucidate the factors governing distribution of a drug and/or contrast medium in the spinal fluid. Funkquist (38) found that in order to insure the passage of contrast medium in dogs from the lumbar region into the cervical area, fluid from the cervical subarchnoid space had

to be removed before injection of the contrast. Also, the neck of the animal had to be in extension during the injection. Rieselbach, et al. (39) instilled 50 microcures of I^{131} rose bengal into the spinal fluid of monkeys, varying the volume of injection so as to comprise 0.7% to 42% of the estimated CSF volume. X-rays of slices of frozen spinal cord and brain revealed the extent of distribution one hour after injection and demonstrated the need to use an injection volume which is 25% of the total CSF in order to have distribution throughout the subarachnoid space. These investigators also studied eight patients in whom radioactive gold was instilled in volumes greater than 10% of the CSF. Two hours later, all patients had basal cistern activity but the patient with the best overall distribution had also received the largest volume, 33% of the estimated CSF. In another patient, rescanning 24 hours later showed distribution over the cerebral convexity consistent with the normal upward flow of CSF from the basal cisterns. The authors note that despite this and other instances of later distribution, effective antibiotic therapy in cases of diffuse meningeal involvement requires immediate optimal distribution because of the relatively rapid decrease in concentration of most drugs (in contrast to gold) after intrathecal administration. Alazraki, et al., (40) studied monkey cisterna magna fluid after the animals had been given a hyperbaric solution containing amphotericin B, $D_{10}W$, and a radioisotope (specific gravity 1.034 compared to 1.006 for CSF). Injection was followed by Trendelenburg

positioning. When compared to a normobaric solution given in the horizontal position, the cisternal concentrations of the first group were 4 times greater at 8 minutes and higher throughout the first 30 minutes, resulting in double the amount of antibiotic in the cisternal fluid within the first half-hour.

In summary, there is experimental evidence for a better intracranial distribution of an intrathecally administered drug when the injected solution is 1) hyperbaric, 2) equal to or greater than one fourth the estimated CSF volume, and 3) followed by Trendelenburg position. These in vivo studies were carried out in patients or animals without meningitis and depend greatly on flow characteristics of the CSF which could be altered by an inflammatory meningeal process. In adults more direct clinical experience is needed to evaluate not only the optimal dose of gentamicin but the optimal site and procedure for injection. In infants easy access to the ventricular fluid via the anterior fontenelle makes the intrathecal versus intraventricular administration preferable.

Toxicity: Since the first patients received gentamicin in 1962, physicians have been looking for and finding incidents of gentamicin toxicity. These have been of four types: 1) acute, immediate toxicities; 2) renal toxicity; 3) vestibular toxicity; and 4) auditory toxicity. To intelligently evaluate the usefulness of this antibiotic, the risk of each known toxic reaction must be measured against the known efficacy of this drug. In addition, the

physician must balance the toxicities of gentamicin against the significant mortality and morbidity rates which accompany gram-negative meningitis in adults and neonates.

Acute toxicity: Initial studies were carried out in mice by Black, et al. (13), establishing an LD_{50} of 430 mg/kg intraperitoneally and 75 mg/kg intravenously which indicated greater "acute toxicity" (undefined by the authors) than kanamycin and less than neomycin. However, the amount needed to achieve serum inhibitory antibiotic levels is 1/10 to 1/20th that of either neomycin or kanamycin. During human clinical trials there have been only scattered reports of immediate toxic reactions. Klein, et al. (3) reported the occurrence of a maculopapular rash in a 43 year old woman being treated for klebsiella bacteremia which cleared within 48 hours after discontinuance of gentamicin. This patient had also been receiving an amphetamine drug and oral iron preparation for more than 3 weeks before the eruption. Later clinical trials have not supported this early single finding, so that the occurrence of a rash in a patient receiving gentamicin should initiate investigation into other possible etiologies. Correspondingly, there have been reports of transient elevations in SGOT (3,22) which have not proven to be clinically significant.

Any intrathecal injection is associated with its own morbidity. Seizures, pain, as well as sensory and motor function loss have followed intrathecal injections, especially in the case of cancer

chemotherapeutic agents such as methotrexate (41-43). When a seizure has followed the use of gentamicin for gram-negative bacillary meningitis, it is often difficult to determine the role of gentamicin in initiating the seizure. Although Newman and Holt (26) obtained neuropathological examination in two infants who died within one hour of the injection, one of whom had convulsions 10 minutes after injection, there was no evidence of damage other than gross hemorrhage. However, as described above, Graybill, et al. (33) did witness seizures and respiratory arrest in an adult immediately following intraventricular infusion. Many other adults and infants have received both IT and IVt gentamicin without acute adverse effects even when mistakenly high doses were given. After 10 years of clinical experience it is apparent that gentamicin is an antibiotic with few acute side effects, even when delivered into the cerebrospinal fluid.

Nephrotoxicity: Several of the first reports on the pharmacology of gentamicin discussed its nephrotoxicity, specifically acute tubular necrosis. Black, et al. (13) found that 50% of rats died after two weeks of 160 mg/kg/d of gentamicin because of frank tubular necrosis. There was less renal pathology with lower doses and at 20 mg/kg/d no clinical, gross or histopathological changes were noted. However, all beagles receiving 40 mg/kg/d and one dog receiving 8 mg/kg/d died as a result of renal tubular necrosis. Klein, et al. (3) noted a rise in BUN in two of twenty-six patients receiving systemic gentamicin with no other apparent

cause for decreased renal function. In 1968 Falco, Smith and Arcieri (44) summarized the clinical experience in animals on the nephrotoxicity of gentamicin as compared to that of other aminoglycosides. They found nephrotoxicity to be greater than that of streptomycin, similar to kanamycin, and less than neomycin or polymyxin. These authors also evaluated 131 patients who had serial BUN values obtained before, during, or after treatment. Only 4 of 68 increases were classed as "probably" related to gentamicin and 16 as "possibly" related. The definitions of these categories are not precise. The authors did state that the "possibly related" category included cases where there was neither positive evidence for gentamicin toxicity nor evidence for any other cause. Of these 20 cases, seven were reversible, 9 occurred in terminally ill patients and 4 had no followup. There was no demonstrable relationship between dose or duration of therapy and nephrotoxicity. The authors estimated the incidence of nephrotoxicity to be 2% or less and ranked it with that of streptomycin. Commenting on this study, Riff (45) also described her experience with 110 patients, 15 of whom were noted to have a BUN rise of 5 mg or greater. The cause of the rise was often difficult to determine. She concluded that the clinical expression of nephrotoxicity is not very important in the use of gentamicin, and added that no late renal damage had been recognized. In 1971 Wilfert, et al., (46) supported the above view with the results of another review of 77 courses of therapy. At this time gentamicin was generally being used in doses twice as

large as during the earlier studies, 3-5 mg/kg/d vs. 1.2-3 mg/kg/d. Five of the 32 instances in which the BUN or creatinine rose were thought due to gentamicin. All of these patients received more than five days of therapy and three patients had slight BUN elevations before therapy, suggesting some prior compromise of renal function. In all of these patients the BUN gradually returned to pretreatment levels.

It would appear that the use of gentamicin in patients with normal renal function rarely produces serious renal damage. However, in patients with elevated BUN or serum creatinine values, who cannot excrete gentamicin at a normal rate, the antibiotic serum level rapidly rises. This rise increases the risk of toxicity at a time when the compromised kidney is unable to compensate for even slight tubular damage. To avoid precipitous renal failure, the BUN and creatinine levels should be noted before and during a course of gentamicin and should be closely monitored in patients with any sign of renal dysfunction.

Ototoxicity: Significant eighth nerve toxicity of gentamicin was manifested in one of the first four patients to receive the new antibiotic. This woman suffered bilateral loss of vestibular function after a course of gentamicin (19). From the beginning, therefore, clinical investigators were sensitive to the ototoxic possibilities, both auditory and vestibular, of this drug.

Animal studies were initiated to evaluate these effects. Black, et al., (13) examined cats for vestibular dysfunction as demonstrated by ataxia and impaired "righting reflex." He found no

evidence for ataxia with doses under 50 mg/kg/day, but did demonstrate ataxia on the fifteenth day with a dose of 50 mg/kg/d. These results, seen also in beagle hounds, were similar to the effects of streptomycin and kanomycin at the same doses. However, since the therapeutic doses of gentamicin are 1/10 to 1/20th those of kanamycin and streptomycin, clinical vestibular toxicity was expected to be correspondingly smaller. In 1969, Hawkins, et al. (47) also demonstrated ataxia in cats with 10-80 mg/kg/day of gentamicin after periods ranging from 13 days with the largest dose, to 113 days with the smallest. On post-mortem examinations of the vestibular apparatus, scarring and loss of hair cells was seen in the macula sacculi. When compared with streptomycin on a weight-for-weight basis, gentamicin was found by these investigators to be twice as toxic for the vestibular system and slightly more toxic to the cochlea. They also invoked the lower dose requirement of gentamicin as hope for a low clinical incidence of ototoxicity. Wersall, Lundquist and Bjorkroth (48) examined, by electron microscopy, the effects of locally applied solutions of gentamicin in the middle ears of guinea pigs. With dilute solutions, 0.3% of gentamicin in saline, they saw degeneration of vestibular and cochlea sensory cells similar to that found after prolonged IV injections. These same findings were later confirmed in cats (49). McGee, Webster and Williams (50) evaluated cat vestibular function by using electronystagomography. After fourteen days of 20 mg/kg/day of gentamicin, depression of post-rotatory nystagmus and of the normal response to caloric irrigation was

observed in 60% of animals. Auditory function damage (measured via alterations in conditioned response patterns) occurred in only 6.6%. Sixty percent of these animals also demonstrated renal toxicity. The incidence of ototoxicity was higher and occurred earlier in this group than in the group without nephrotoxicity. Waitz, et al. (51) demonstrated in cats that renal and vestibular toxicity could be separated temporally with low doses, 20 mg/kg/d where the vestibular dysfunction occurred before the renal. They also found that ataxic cats with evidence of renal impairment reversed this dysfunction within twenty days of stopping the antibiotic but remained ataxic for forty-five days. At this time gentamicin was resumed and death from renal tubular necrosis followed in 16-19 days. Igarashi and coworkers (52) did similar experiments with squirrel monkeys using proficiency at moving along a rotating rail as their measure of ataxia. Decreased proficiency correlated with damage, seen histologically, to vestibular hair cells and in some cases degeneration of afferent nerve endings around the hair cells. They, too, demonstrated renal damage in almost every animal. It consisted of slight to severe tubular degeneration with glomerular changes in some animals. As with all other animal studies, high daily doses produced early severe renal damage.

The first 27 patients who developed ototoxicity were reported at the First International Symposium on Gentamicin in Paris, 1967 (53). Clinical characteristics common to this group included

age over 60 years, previous use of other ototoxic drugs, renal insufficiency, and plasma concentrations of gentamicin over 12 µg/ml. In 1971, Jackson and Arcieri (54) reviewed the total experience in the United States in which gentamicin was reported to have possibly caused ototoxicity. They compared the clinical characteristics of these patients and details of 70 courses of gentamicin therapy to 843 gentamicin regimens without ototoxicity. In 20 patients there was prior otologic disease, nonvestibular dizziness, transient symptoms, or symptoms with normal vestubular function tests. Two patients were critically ill or poorly responsive and four were also receiving kanamycin or streptomycin. These patients combined gave a total of 26 cases classed as doubtful or insignificant gentamicin toxicity. The 44 remaining cases of ototoxicity were thought to be "probably caused by gentamicin." Two-thirds of this group had only vestibular symptoms, one-sixth had only auditory dysfunction and one-sixth had both types of ototoxicity. It should be noted that 14 of the 37 patients who developed signs and symptoms of vestibular dysfunction had only transient impairment. Animal studies have produced conflicting opinions on whether ataxia was permanent. Webster, et al. (49) demonstrated recovery of post-rotatory nystagmus and of normal electronystagmographic measurements in at least two cats kept six months after courses of topical middle ear applications of gentamicin. Recovery of caloric response six months after a course of systemic gentamicin was also demonstrated on 40% of the cats studied by McGee, et al. (50). However, Waitz, Mors and Weinstein (51) stated that the vestibular

damage "appeared to be irreversible." The three cats they tested were given a course of 40 mg/kg/day which was twice the dose used in the above two studies where vestibular recovery was demonstrated. Also, these animals were only allowed forty-five days to recover before having the gentamicin regimen resumed to the point of renal tubular necrosis and death. All three cats were ataxic for the forty-five days but this fact does not support their conclusion of "irreversible" vestibular damage especially when compared to the 6 months needed for recovery in the Webster (49) and McGee (50) studies. In light of these experiments, it would be interesting to know the recovery time of the 14 patients described by Arcieri and Jackson (54).

In an attempt to determine factors of general importance in the development of human ototoxicity, Jackson and Arcieri (54) performed a stepwise discriminant function analysis which revealed one outstanding difference between patients suffering gentamicin ototoxicity and the control group. Persons with eighth nerve damage had a significantly higher incidence of impaired renal function ($p < .0001$). In addition, of the ototoxic patients with renal impairment, 35% had had prior courses of ototoxic antibiotics whereas none of the persons with renal impairment but without ototoxic manifestations had received similar prior therapy. Total dose was not found to be significantly different between groups nor was the number of days of treatment. Age, which earlier had been thought to have a direct correlation with increasing toxicity (53) was not found to be an important factor by these investigators, who eliminated many untested or poorly tested children from the

control sample, and then compared this group with the 70 suspected cases of ototoxicity and found no significant age difference between the groups. Jackson and Arcieri summarized their data by stating 1) that the true incidence of gentamicin ototoxicity over a four-year period in the U.S. (1966-1969) is 2%, 2) that the overwhelmingly important factor in the occurrence of eighth nerve dysfunction in any one patient is that patient's renal function, and 3) that only in cases of renal insufficiency were previous courses of ototoxic antibiotics a risk factor. Because increasing daily dose per kilogram and not total dose were related to ototoxic effects, they also felt that toxicity must be related to serum concentrations. They noted that over 50% of the ototoxic group but only 22% of the control group had concentrations over 8 ug/ml, and recommended monitoring serum levels of gentamicin (54).

The toxicities of systemic gentamicin have been better understood by extensive and often elegant animal and human studies. They allow the clinician using this drug not only to know the incidence of life-threatening or especially prominent adverse effects, not only to see examples of the disruption on an electron-microscopic level, but also to understand which factors in his own patient enhance the risk of toxicity. The physician then has monitoring techniques to create a personalized regimen for this patient.

When gentamicin is administered directly into the CSF, are the known toxicities more severe? Are there new toxic effects to CNS tissues? During a discussion in the 1971 gentamicin symposium, Hawkins stated that

> "the intrathecal route offers a direct line of communication by way of the perilymphatic duct and cochlear aquaducts to the basal turn of the cochlea. We have found in cats (and I would not want to overstress the applicability of animal experiments to these matters) that the dose of streptomycin and neomycin required to produce severe ototoxicity when given by the intracisternal route is of the order of 1% of that required by the intramuscular route." p.S620 (55).

Considering the possibility that gentamicin is analogous to streptomycin and neomycin, and that human ears are analogous to those of cats, Hawkins's comments give rise to worry over the toxic effects of any intra-CSF gentamicin regimen. The present neonatal and infant studies do not contain followup evaluations of the child's vestibular and auditory function. Followup in adult meningitis patients has also been poor, although several patients with CSF concentrations equal or above those of the serum have been said to recover without neurological sequelae. To understand whether intrathecal or intraventricular gentamicin enhances ototoxicity, more clinical studies with long-term followup are required.

Present Investigation

The purpose of this study was to provide additional clinical information about the efficacy and toxicity of intrathecal (IT) and intraventricular (IVt) gentamicin when used in patients with gram-negative bacillary meningitis. An investigational preparation of gentamicin in saline without the usual chelating agent, anti-oxident, and paraben preservatives was given to patients intrathecally or intraventricularly. The efficacy and toxicity of this preparation was compared to those of commercial gentamicin administered in the same way.

Three areas of investigation were concentrated on in this study.

A. Patients receiving the investigational preparation had multiple CSF and serum gentamicin assays performed during antibiotic therapy. These determinations provided opportunity to correlate 1) dosage with CSF concentration, 2) CSF concentrations over time, 3) and serum levels with CSF levels.

B. Efficacy in all cases of meningitis treated with gentamicin was analyzed not only in terms of the investigational or commercial preparation used but also according to the age of the patient, the infecting organism, and the concurrent use of additional antibiotics. The regimen including intrathecal or intraventricular gentamicin in treating gram-negative bacillary meningitis at Yale New Haven Hospital was then compared to regimens using only systemic antibiotics.

C. Toxicity was evaluated through review of the patient's hospital course and followup examinations. Particular attention was paid

to any evidence for acute, renal, vestibular, or auditory toxicity for either the investigational or commercial preparation.

Materials and Methods

Patients: Nineteen patients, 11 adults and 8 infants, with suspected gram-negative meningitis were treated with intrathecal and systemic gentamicin alone and with other antibiotics.

After protocol approval by the Yale University Human Investigation Committee, an investigational preparation was made available for use. The protocol delineating both intrathecal or intraventricular and systemic gentamicin treatment was fully explained to the responsible person in each case and a signed consent form was obtained before initiation of therapy. All patients receiving the investigational preparation intrathecally or intraventricularly also received concomitant commercial gentamicin intramuscularly in a dose of 3-5 mg/kg/day. Eleven patients, 6 adults and 4 infants with bacteriologically proven meningitis due to a gram-negative organism, and one adult with suspected meningitis, were given the investigational preparation.

For comparison, the charts of all previous Yale-New Haven Hospital patients who received the commercial gentamicin preparation intrathecally or intraventricularly were reviewed. Eight patients, 4 adults and 4 infants including one infant without culture positive CSF infection, received the commercial preparation.

In the investigational group, CSF gentamicin concentrations were then correlated with dosage, duration of therapy, and serum levels. All cases of bacteriologically proven meningitis in both the investigational and commercial groups (18 cases in 17 patients) were analyzed according to cure rate in comparison with the type of infecting

organism, age of patient, and use of additional antibiotics. Acute toxic reactions in addition to renal and ototoxicities were evaluated in all patients of both the investigational and commercial groups (19 patients). Comparisons of efficacy and toxicity were then made according to the preparation used.

Investigational Preparation: Gentamicin sulfate in saline (2 mg/cc) was provided by Dr. George Arcieri of Schering Corp. In contrast to the current commercial preparation, this solution does not contain 1) the chelating agent, disodium ethylenediamine-tetra-acetate dihydrate, 2) the antioxident, sodium bisulfate, nor 3) the preservatives, methyl and propylparabens. Recommended intra-CSF doses were 1-2 mg/24 hrs in infants and 2-4 mg/24 hrs in adults. The drug was administered by barbatage and vital signs monitored during the slow infusion.

Bioassay: The method of Winters, Litwack, and Hewitt (56) as modified in our laboratory was employed to determine gentamicin levels. This method utilizes an agar-diffusion assay which requires only small quantities of body fluids (0.02 ml Serum or CSF) and affords results within 5 hours. A standard solution of gentamicin sulfate in distilled water is made monthly and frozen. Concentrations of 20, 10, 5, 2.5, 1.25 and 0.625 ug/ml are made which are suitable for linear regression calculations. The test organism is Bacillus globigii, an unclassified spore-former with a MIC of gentamicin of 0.5 ug/ml. It is maintained on nutrient agar slant (DIFCO)

and transferred weekly. The organism is prepared by transferring a few colonies to 30 ml of brain-heart-infusion broth and grown for 6 hours at 37°C resulting in approximately 10^7-10^8 organisms per ml. To prepare the plates, 3 ml of this 6-hour culture is added to 36 ml of modified tryticase soy agar (BBL). (Modification--26.66 gm. of agar are added to 1000 ml of distilled water giving a final pH of 7.3). Thirty-six ml of this mixture is poured into petri dishes and allowed to solidify. It is further cooled by refrigeration for 15 minutes. If the patient has received any of the penicillins, 1.0 ml of penicillinase (DIFCO) is added to the mixture before cooling. If the patient is receiving oxacillin or a cephalosporin, another organism, Enterobacter aerogenes is used in place of Bacillus globigii for the bioassay. This organism is resistent to oxacillin and produces a cephalosporinase. However, this cephalosporinase has recently been found not to inactive cefazolin. Therefore, when the patient is receiving cefazolin, 1 ml of reconstituted beta lactamese, broad spectrum mixture (Whatman) is added to each plate in order to inactivate cefazolin. Wells produced with a blunt 4 mm diameter bore are filled in duplicate with the standards and the patients serum or CSF, using a nonheparinized capillary tube. The plates are then incubated overnight at 37°C. The diameter of the zone of inhibition is read for both standards and unknown with a millimeter ruler. The concentration of the antibiotic standards (µg/ml) with its mean inhibition zone diameter (mm.) as well as the unknown's mean zone sizes are

entered on a Monroe calculator which then computes the concentrations of the unknown through linear regression analysis.

Results

A. CSF gentamicin concentrations: Cerebrospinal fluid obtained 24 hours (± 2 hrs.) after intrathecal or intraventricular instillation of 3 or 4 mg. of gentamicin in adults and 1 or 2 mg. of gentamicin in infants, resulted in 33 determinations ranging from 1.35 µg/ml to 24.3 µg/ml with a mean of 6.69 µg/ml. These determinations, referred to as 24 hr. CSF concentrations, were made from day 2 to day 16 of IT or IVt therapy. In order to study the 24 hr. CSF levels over the course of therapy, gentamicin concentrations were plotted for individual patients over time (fig. 1). Although the same regimen of gentamicin therapy was continued in these patients, 24 hr. CSF levels of gentamicin were noted to decrease over time. All 24 hr. CSF concentration values were graphed according to day of intrathecal or intraventricular therapy, fig. 2. Concentrations on Days 1-6 were found to be significantly higher than those on Days 7-13 ($p < .001$) (mean days 1-6 = 9.168 µg/ml SE = 1.36, mean days 7-12=3.149 µg/ml SE= .65). In no patient was there an indication of gentamicin accumulation in the CSF over time. In order to determine whether there were changes in opening pressure of the lumbar punctures over the course of therapy which were related to the decreasing CSF gentamicin levels, opening pressures were plotted over time in six patients (fig. 3). No trend in these pressures over the course of therapy was observed.

In several instances, CSF and serum samples were drawn from the same patient at the same time. The cerebrospinal fluid and serum were obtained 24 hours (± 2 hours) after the last intrathecal or

intraventricular dose and 4-6 hours after the previous systemic dose. Linear regression analysis of the simultaneous concentrations revealed no significant correlation between the CSF and serum values ($r = .44$). In addition, the interval between the last systemic dose of gentamicin and withdrawal of the CSF sample was plotted against the gentamicin concentration in that CSF sample in order to investigate any possible effect of systemic gentamicin therapy on 24 hr. CSF levels (fig. 4). As shown in figure 4 the number of hours after systemic administration did not affect the 24 hr. CSF levels. Finally, in order to look at the effect of intrathecal or intraventricular gentamicin administration on serum levels in our patients as compared to serum profiles of gentamicin concentrations reported earlier in the literature, serum concentrations at varying intervals after systemic dosage are illustrated in fig. 5. The serum profiles in our patients do not differ from the range reported in patients who did not receive CSF instillation of the antibiotic (20,5,6).

B. Efficacy: Eighteen cases of meningitis in seventeen patients, ten adults and seven infants, were bacteriologically proven to be caused by gram-negative bacillary organisms. One newborn suffered reinfection (*Proteus Mirabilis* then *E. coli*) accounting for the eighteen meningeal infections in seventeen patients treated with intrathecal or intraventricular gentamicin. Thirteen bacteriologic cures were obtained (72%). The patient's age, infecting organism, and number of days of IT or IVt therapy required to sterilize the CSF are shown in Table 1.

Table 1

Investigational preparation:

Patient	Age	Organism	# Days to sterile CSF	
A.P.	59	Klebsiella	13	
W.P.	56	Klebsiella	1	
H.D.	35	Proteus Mirabilis Bacteroides	5	
M.M.	45	Ps. Aerugenosa	2	
D.C.	58	E. coli	7	
C.L.*	31	Pseudomonas & Proteus Mirabilis	-	(last CSF before death sterile but signs of active infection present at autopsy)
B.L.	Newborn	Proteus Mirabilis	11	
D.L.*	1 mo.	E. coli	12	(but then relapse)
B.C.*	Newborn	Ps. Aerugenosa	-	(Antib. D/Cel)
L.C.**	Newborn a)	Proteus Mirabilis	3	
	b)	E. coli	7	

Commercial Preparation:

V. D	60	E. coli	1	
A.G	57	E. coli	10	
N.P*	42	Klebsiella	-	
G.R	23	Ps. Aerugenosa	4	
S. H	9 mo.	Flavobacter	5	
A.M.	2 mo.	Klebsiella	4	
G.C.*	Newborn	E. coli	-	

*Treatment failures

**Reinfection - 2 courses of therapy

There was no difference in the bacteriologic cure rate between patients who received the investigational preparation and those treated with commercial gentamicin (Table 2).

Table 2

	Gentamicin			
	Investigational		Commercial	
	Cures	Failures	Cures	Failures
Adult cases	5	1	3	1
Infant cases	3 (in 2 infants)	2	2	1
Totals	8	3	5	2
% cured	73%		71%	

Eleven of the seventeen patients with bacteriologically proven meningitis survived the hospitalization (6 adults and 5 infants). This group differed from the one designated as "cures" (8 adults and 4 infants) in the following ways: one adult (A.P.) whose Klebsiella meningitis was cured, died one month later after a second surgical procedure for removal of a frontal meningioma; a second adult (D.C.) died suddenly three months after cure of his E. coli meningitis while awaiting nursing home placement; one infant who suffered from hydrocephalus, had sterile CSF 12 days after initiation of IVt gentamicin therapy for E. coli meningitis, but then suffered a relapse which was successfully treated with chloramphenicol. Therefore, this infant was considered a gentamicin treatment "failure" but survived the hospitalization.

The infecting organisms, number of cures and treatment failures are shown in Table 3. Treatment failures occurred with Klebsiella and E. coli infections as well as a mixed Pseudomonas and Proteus M. infection. The infant with Ps. aeruginosa meningitis complicating a meningomyelocele was considered a treatment failure for this study. However, antibiotic therapy was discontinued after four days of treatment. The baby did live an additional 22 days with no systemic signs of meningitis (fever or seizures) but no further CSF samples were obtained.

Table 3

Organism	Cure	Failure	Total	% Cured
E. coli	4	2	6	66
Klebsiella	3	1	4	75
Ps. Aeruginosa	2	1	3	60
Proteus Mirabilis	2	0	2	100
Flavobacter	1	0	1	100
Proteus Mirabilis & Bacteroides	1	0	1	100
Pseudomonas & Proteus Mirabilis	0	1	1	0
Total	13	5	18	72%

In eleven of the thirteen cured cases of meningitis, antibiotics in addition to gentamicin were given concurrently. In order to further delineate the effect of these additional antimicrobial

agents on the successful treatment of these infections, the eleven cases were divided into those receiving "effective" and "noneffective antibiotics. This separation was made according to in vitro sensitivity studies and the ability of the additional antibiotic to penetrate the CSF. Using this criteria, seven patients were in the "effective" antibiotic group (64%). Six patients comprised the "noneffective" group including one patient who received chloramphenicol but whose Pseudomonas organism was not sensitive to that drug, 3 patients receiving antimicrobials which do not penetrate the CSF, and two patients who received only gentamicin. Therefore, in six of thirteen instances (55%) treatment success could be specifically attributed to intrathecal gentamicin.

In addition to meningitis, patients had a wide range of underlying diseases or congenital defects. Eight of ten adults had a prior neurosurgical procedure. The ninth adult patient had an automobile accident resulting in a basilar skull fracture, and the tenth suffered from diabetes mellitus, alcoholism, and septicemia in addition to gram-negative bacillary meningitis. Four of the seven infants had meningomyeloceles and/or hydrocdphalus. Two of the remaining three infants were premature and the other was considered normal when delivered at term.

In order to compare the efficacy of antibiotic regimens which included intrathecal or intraventricular gentamicin with solely systemic antibiotic therapies, all cases of gram-negative

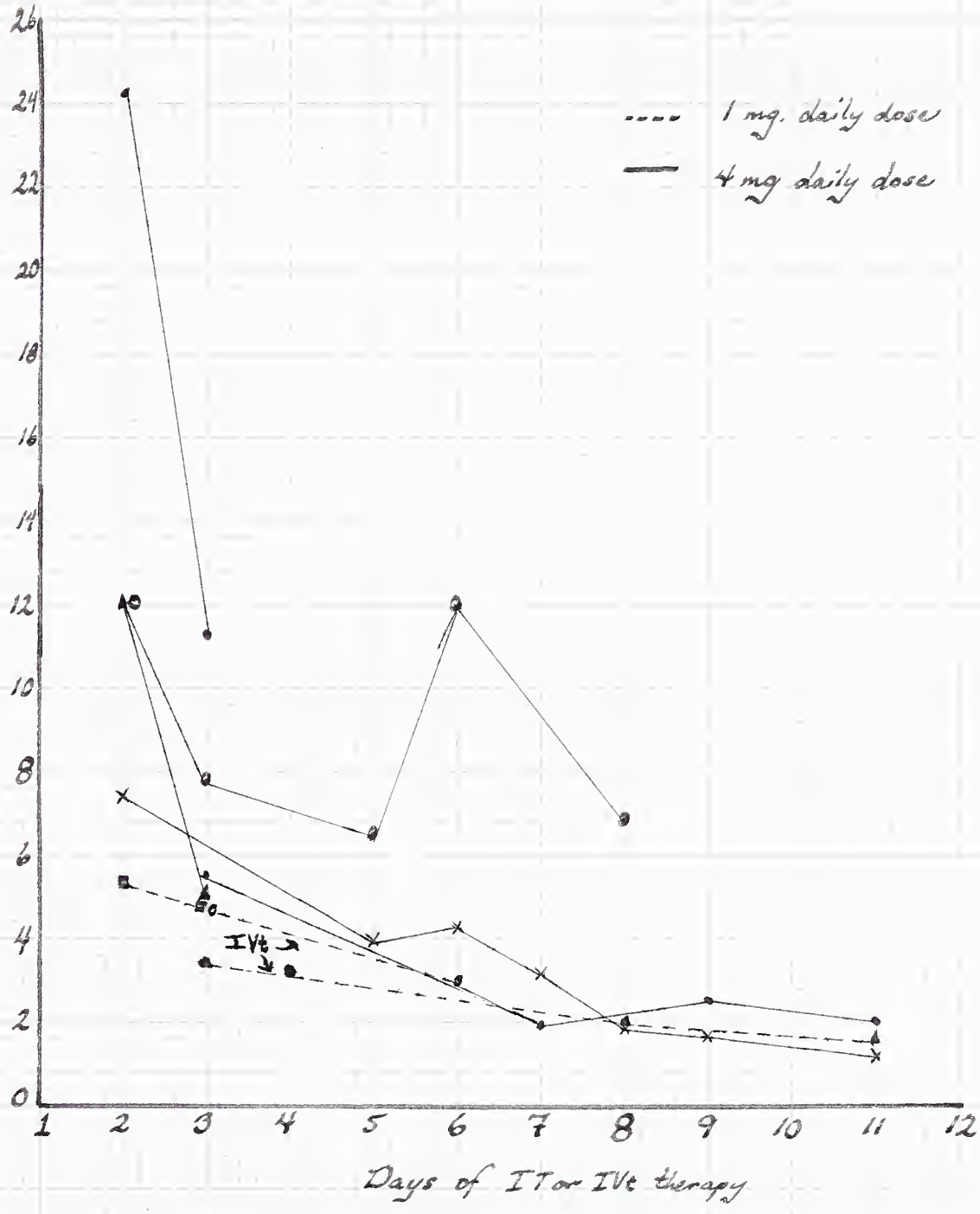
bacillary meningitis at the Yale affiliated hospitals were reviewed between the period of September 1968 and June 1974. To partially minimize the variation in treatment methods, analysis was restricted to only those cases in which either the systemic regimen or the intrathecal gentamicin regimen was begun promptly (within 48 hours) after isolation of the CSF organism. Nine failures occurred in 20 cases treated with only systemic antibiotics (45%). Two treatment failures occurred in thirteen cases treated with IT or IVt gentamicin (15%). This difference was not statistically significant ($p < 0.20$), however the trend indicated that better therapeutic results are obtained when intrathecal or intraventricular gentamicin is part of the antibiotic regimen.

C. Toxicity:

Renal toxicity was evaluated in 19 patients treated with gentamicin both IT and IVt in terms of abnormal BUN and creatinine values during or immediately after termination of gentamicin therapy. On this basis, none of the nineteen patients experienced renal toxicity. No acute toxicity during or immediately after the instillation of gentamicin was observed in 18 of 19 patients including one adult who inadvertently received 20 mg II during one injection. One woman did develop bilateral lower extremity pain and muscle spasm during intrathecal gentamicin administration and later during intrathecal instillation of Polymyxin B. After discharge the patient complained of lower extremity weakness, and was noted to have bilateral weakness of flexor muscles of the

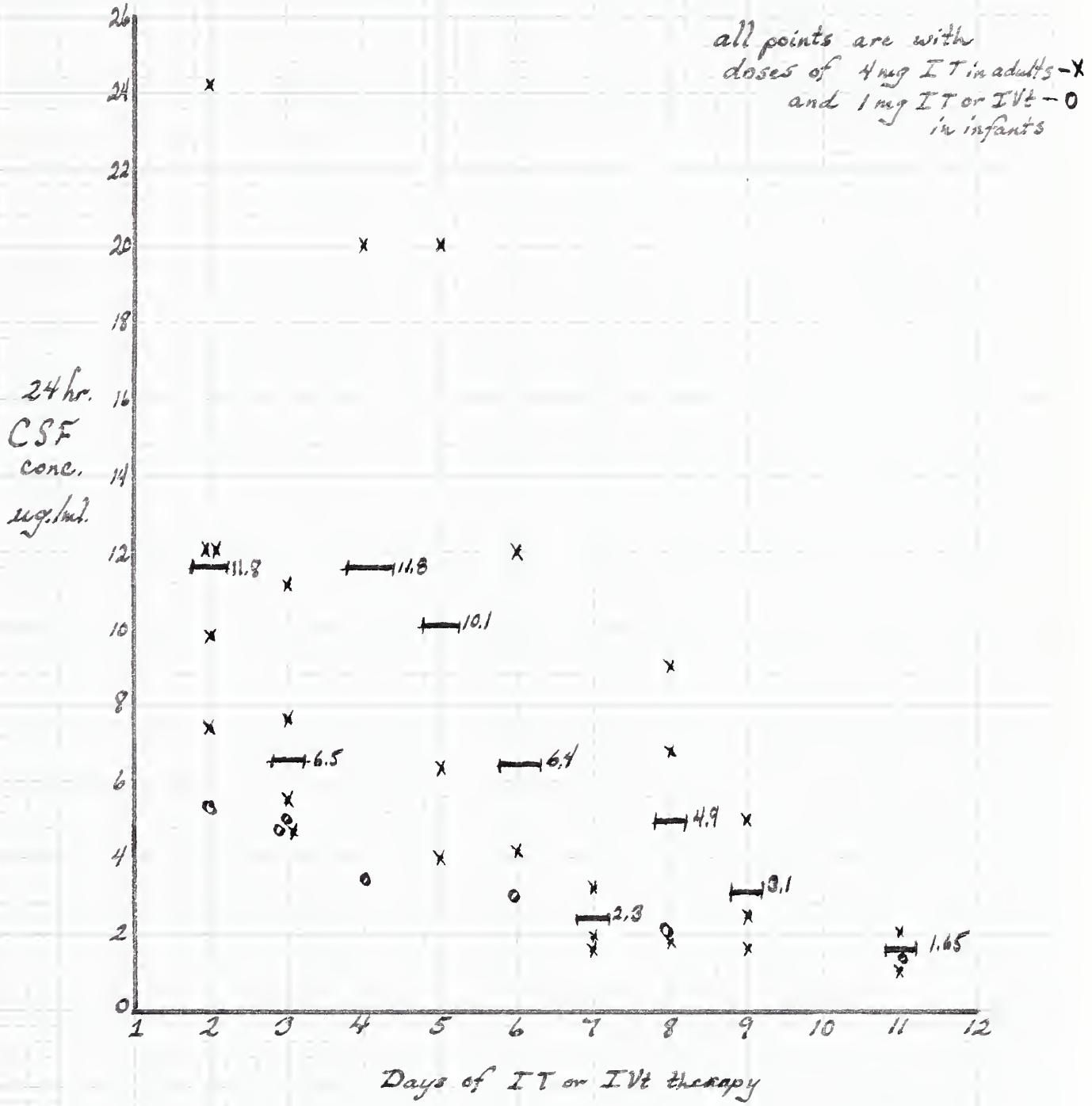
hip as well as sensory loss from S2 to S5. Evaluation of this problem was complicated by her underlying disease, metastatic breast cancer, which caused her death four and one-half months after discharge.

Ototoxicity, both auditory and vestibular, was extremely difficult to evaluate during hospitalization because of the desperately ill condition of these patients and the fact that 8 of 19 were infants. However, no clinical evidence of clear gentamicin toxicity was noted in eight patients, 5 adults and 3 infants, who were followed for four months to 3 years after intrathecal therapy. Two adults and 2 infants of this group received the investigational preparation. Three adults and one infant received the commercial preparation. No difference in toxicity was noted between the investigational and commercial preparations. Three patients were lost to followup. One of the children was noted to have a broad gait 2 years after therapy. This could be considered as evidence for gentamicin induced vestibular damage. However, the child had had surgical exploration of the posterior fossa during which a portion of cerebellum containing the dentate nucleus was removed. Another infant remains severely retarded, cortically blind and without control of her lower extremities, bladder or bowel function 3 years after a protracted hospital course for meningomyelocele repair and multiple ventricular shunts. She could not be evaluated for long term toxic effects of gentamicin therapy.



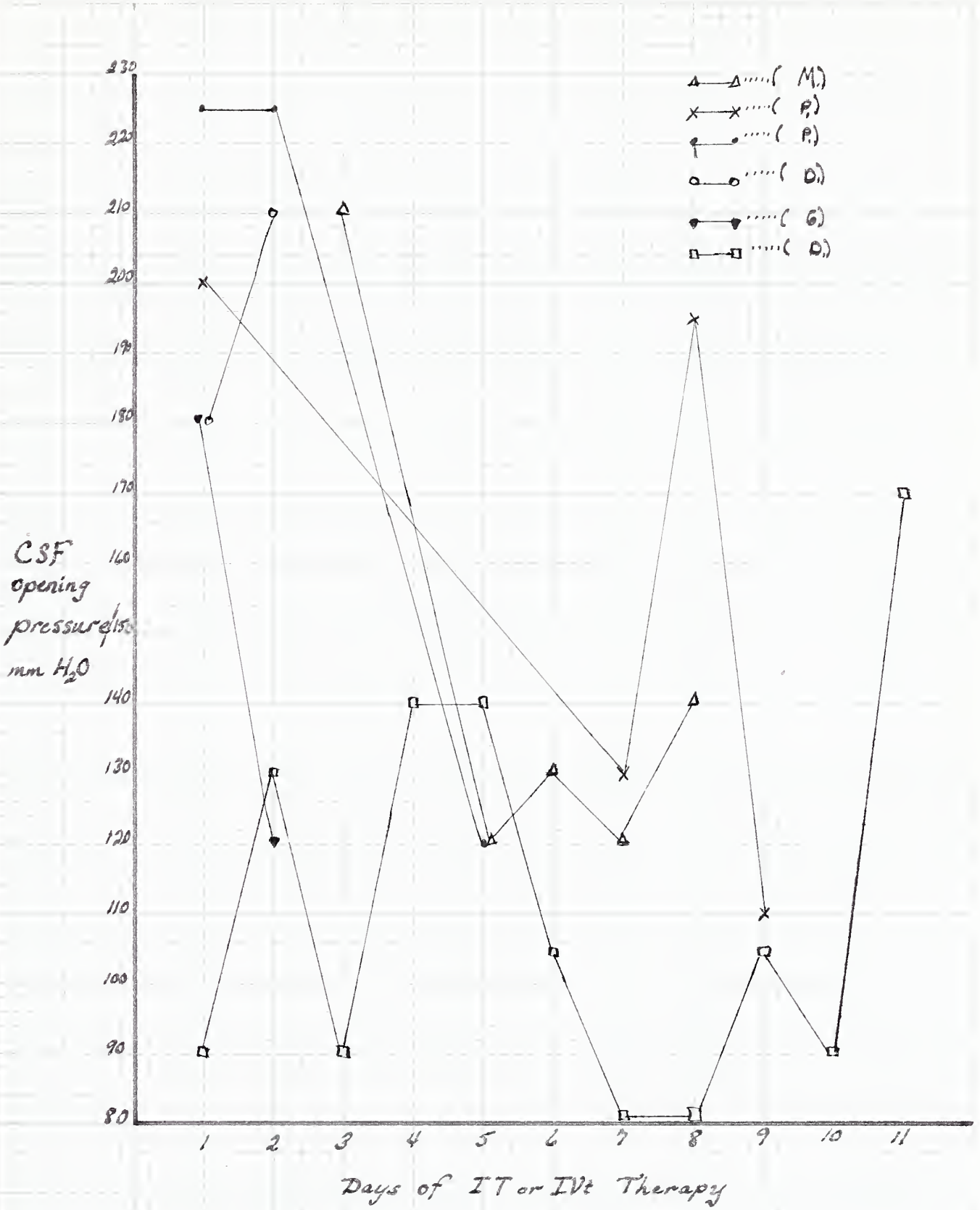
24 hr. CSF conc. over the course of therapy for patients with >1 determination

Fig 1.



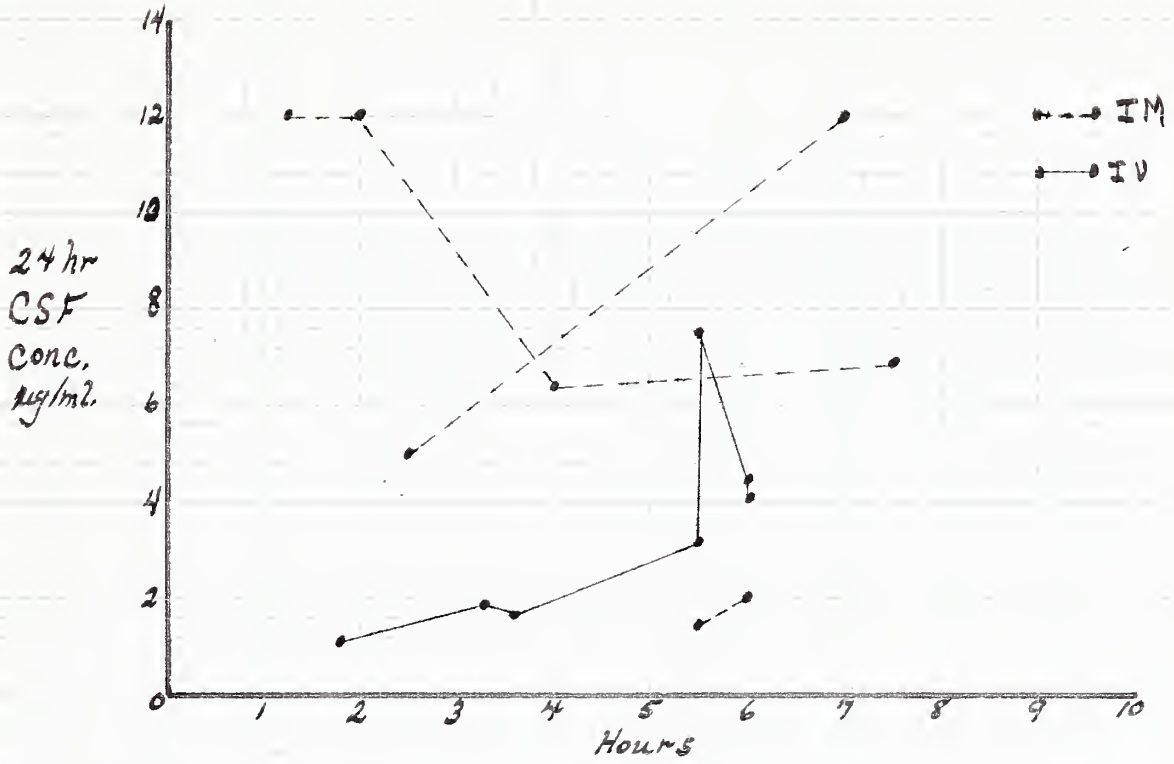
24 hr. CSF concs and means for successive days of therapy

fig 2



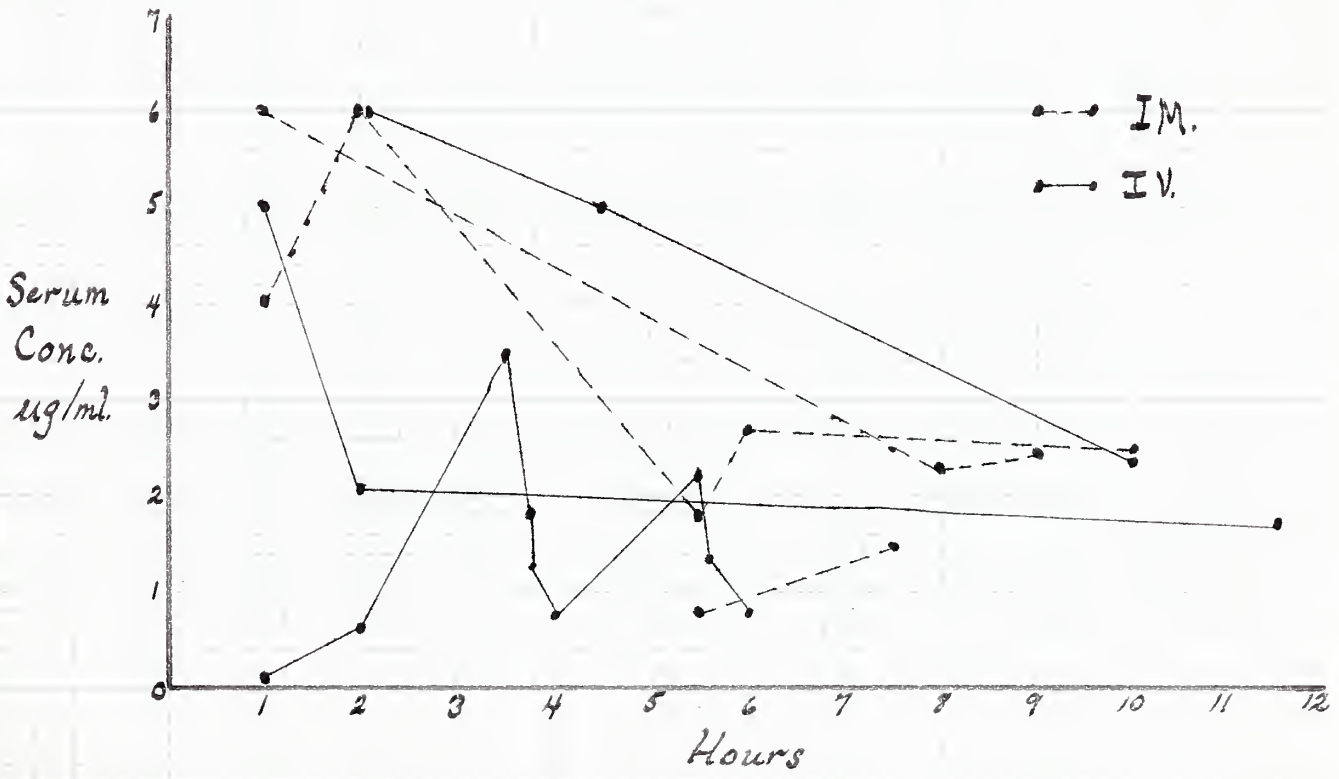
Opening CSF pressure on successive days of therapy

fig 3



24 hr. CSF concentrations vs. time after systemic dose

fig 4



Serum concentration vs. time after systemic dose

fig 5.

Discussion

The ability to measure by bioassay, concentrations of gentamicin over the course of therapy has demonstrated a surprising range of 24-hour CSF concentrations in patients receiving equivalent doses. Previous studies, usually on a smaller number of patients, corroborate the wide range of CSF concentrations which may be expected even though equivalent doses of 4 mg in adults and 1 mg in infants are given intrathecally or intraventricularly. (25,26,27,30,36,37).

The issue of transfer of gentamicin from serum to CSF or vice versa, was speculated upon extensively in the early literature on gentamicin placement in the CSF (14,20,23). When simulteneous serum and CSF values were compared in our patients, no significant correlation between the two levels was observed. In addition, systemic administration of gentamicin was not noted to affect CSF concentrations, and intrathecal or intraventricular administration of the antibiotic did not alter our patient's serum levels from the profiles described by Winters, et al. (56) and Rodriquez, et al. (20).

Rahal, et al. (36) recently observed a rapid decline in CSF concentrations during the initial 24 hr. period in 21 patients receiving IT gentamicin. Two-thirds of their samples drawn at 20 hours post instillation contained less than 3 μg/ml. This finding caused these authors to conclude that, "Intrathecal injections of 4 mg of gentamicin must be repeated at least every

18 hours to maintain therapeutic concentrations in lumbar cerebrospinal fluid." p. 1394 (36). Their findings and conclusion are not supported by our data. Twenty-three of 33 CSF gentamicin levels (70%), determined at 24 hours (± 2 hours) after the previous intrathecal or intraventricular dose of 4 mg in adults and 1 mg in infants, were above 3 μg/ml. The mean of 6.69 μg/ml and median of 5.0 μg/ml were also well above the values reported by Rahal, et al. (36). On the basis of our data, doses of 4 mg IT in adults and 1 mg IT or IVt in infants every 24 hours gives adequate CSF levels (> 3 μg/ml) in 70% of samples. We, therefore, do not feel that instillation every 18 hours should be adopted as standard therapy. However, we strongly recommend that direct monitoring of CSF concentrations be performed in all patients.

The fact that concentrations in the CSF decreased significantly over the course of therapy in our patients is an interesting although not readily explainable finding. The previously cited studies on the flow of CSF and distribution of labeled molecules within the fluid indicate that a lumbar injected material may have minimal diffusion if injected in a small volume (38,39,40). If a similar method was used each day for a particular patient, then an intra-cerebral change must be postulated for altered distribution and/or excretion of the gentamicin as the meningitis improves. When gentamicin was deposited intra-ventricularly in two infants, 24 hour concentrations over several days did not show

declines similar to those of adults receiving IT injections. Perhaps then, tissue inflammation and low grade obstruction prevents normal flow and dispersal of the drug throughout the CSF at the onset of treatment. But excretion of CSF at the arachnoid villi could also be decreased by the same mechanism. Davson (57) has described the arachnoid villi as made up of aggregates of tubes which open or collapse according to pressure, operate as a valvular mechanism. In monkeys the critical pressure difference is 25-50 mm of saline. These villi allow passage of virtually any size particle including large proteins. Rall and Zubrod (58) in their review of the mechanism of passage of drugs in and out of the CSF, noted that several investigators demonstrated active absorption of organic acids from the CSF. This absorption was localized to the choroid plexus in the fourth ventricle. They suggested that a similar mechanism of removal of organic bases from the CSF might also exist, and noted the similarity between the choroid plexus and the renal tubule. Andriole (59) has noted that the aminoglycosides behave as weak bases. Whether gentamicin might actively be absorbed from the CSF via the choroid plexus is not known, but this might be a factor in the variable concentrations obtained with a standard dose. However, without excretion studies in animals with meningitis, using labeled gentamicin, no definitive explanation for this statistically significant decline can be given at this time.

The efficacy of a regimen containing IT or IVt gentamicin against a variety of gram-negative organisms is demonstrated by bacteriologic cure in 72% of our cases. As observed above, this rate is higher than that of previous regimens employed at this hospital and even in this small group of patients comes close to attaining statistical significance. By separating the "cured" cases into those receiving effective and noneffective additional antibiotics, 55% of the bacteriologic cures could be directly attributed to gentamicin administration. The infant mortality rate of this study was 2 of 7 patients with bacteriologically proven infection. One child died within 24 hours of overwhelming E. coli sepsis and meningitis, the other death occurred 22 days after discontinuance of antibiotic therapy and at that time the child showed no clinical evidence of CSF infection. Excluding the latter case, the gentamicin treated infants had an 80% survival rate which is definitely higher than those of earlier studies. Groover et al. (60) reported an 11 year review in which 41% of purulent newborn meningitis was caused by gram-negative organisms and 81% of these infants died as a result of their infection. An earlier report by Ziai and Haggerty (61) included 83 cases of meningitis with 62 deaths and 30 of 77 cases with culture positive CSF were due to gram-negative bacilli. Although an overall impression of improvement in survival rates with intra-CSF gentamicin is probably justified, it is very difficult 1) to compare studies done in different institutions at different times often with

differing doses of antibiotic, 2) to compare studies done in the same institution when the patients differ not only in their own risk and host defense factors but in the various neurosurgical procedures they have experienced,and finally 3) to compare the role of one drug when it is used in combination with several other antibiotics against a variety of organisms. Dissection of this tangle of variables cannot be accomplished until many more patients, treated with fewer regimens, are carefully studied. Certainly the data presented here provides additional evidence favoring prompt treatment of gram-negative bacillary meningitis with IT or IVt gentamicin.

The only toxicity observed in the 19 patients who received CSF instillations of gentamicin in this study was that of acute pain in the lower extremities in one adult patient when she received either intrathecal gentamicin or intrathecal Polymyxin B. As described earlier this woman continued to have pain and dysfunction of her lower extremities as an outpatient. This was attributed to nerve root inflammation and destruction caused by IT antibiotics. When she died 1 month later because of widely disseminated breast cancer, the diagnosis of toxicity rather than metastatic damage was less certain. This case is one example of the difficulty in attributing any sensory or motor loss in a neurosurgical or neonatal patient with meningitis to the toxicity of the antibiotic. To obtain an accurate audiogram in a desperately ill adult is impossible, in a neonate unproductive, and in an adult with suspected but untested prior diminished acuity, meaningless. It is

equally difficult to accurately test for vestibular ataxia or nystagmus under these conditions. Surveillance for any sign of renal failure followed by appropriate dosage and adjustment has been shown to be the most important factor in prevening eighth nerve toxicity when gentamicin is given systemically (54). The absence of auditory and vestibular toxicity then is not surprising in this group of patients who were without renal dysfunction. Followup studies from 4 months to 3 years in eight patients (5 adults and 3 infants) provide some of the longest post-gentamicin evaluation periods recorded in the literature on IT or IVt gentamicin. The fact that these 8 patients suffered no toxicity indicates that CSF concentrations often above 10 ug/ml at 24 hours and presumably higher soon after the instillation, can be well tolerated in both adults and infants. The ototoxicity feared by Dr. Hawkins with CSF concentrations merely 1% of serum levels producing rapid vestibular dysfunction in animals (55) was not seen in this study. In fact we have no evidence to indicate that gentamicin in the CSF at or above usual serum levels is any more toxic than the systemically delivered drug.

Conclusions

Intrathecal or intraventricular daily doses of 4 mg of gentamicin in adults and 1 mg. in infants was found to produce a wide range of antibiotic concentrations (24.3 to 1.34 ug/ml) in CSF fluid withdrawn 24 hours later.

Instillation of gentamicin into the CSF did not appear to affect serum concentrations. Serum profiles in our patients corresponded to those described previously in the literature. In addition, intramuscular and intravenous administration of gentamicin did not affect 24 hour CSF levels in a predictable fashion.

Daily doses of 4 mg IT in adults and 1 mg IT or IVt in infants produced therapeutic levels (3 ug/ml) in 70% of CSF samples drawn 24 hours later. Data obtained in this study do not support the previous recommendation by others that instillation is required every 18 hours. If possible, each patient's infection should be managed with serial monitoring of serum and CSF concentrations.

CSF concentrations of gentamicin decreased significantly over time even though the patient received the same daily intrathecal dose.

A regimen including instillation of gentamicin into the CSF cured 72% (13 of 18) of gram-negative bacillary infections treated in

this study. This cure rate was higher than that of previous systemic antibiotic regimens (45%) used in this hospital. No difference in efficacy was demonstrated between the investigational and commercial gentamicin preparations.

Within the limits of this study, no evidence of vestibular, auditory, or renal toxicity was found during or after therapy with either the investigational or commercial gentamicin preparation. One patient reported pain during intrathecal administration of the investigational preparation and also when receiving intrathecal Polymyxin B.

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